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### Citation for published version:

Crim, C, Anderson, JA, Calverley, PMA, Celli, BR, Cowans, NJ, Martinez, FJ, Newby, DE, Vestbo, J, Yates, JC & Brook, RD 2020, 'Pulse Wave Velocity in Chronic Obstructive Pulmonary Disease and the Impact of Inhaled Therapy (SUMMIT): A Randomized Double-blind Clinical Trial', *American Journal of Respiratory and Critical Care Medicine*. <https://doi.org/10.1164/rccm.201908-1639LE>

### Digital Object Identifier (DOI):

[10.1164/rccm.201908-1639LE](https://doi.org/10.1164/rccm.201908-1639LE)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Peer reviewed version

### Published In:

American Journal of Respiratory and Critical Care Medicine

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## **Pulse Wave Velocity in Chronic Obstructive Pulmonary Disease and the Impact of Inhaled Therapy (SUMMIT): A Randomized Double-blind Clinical Trial**

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**Author Contributions:** During the development of the manuscript, JAA and NJC were involved in data analysis/interpretation; CC, JAA, and JCY were involved in the study conception/design, the acquisition of data, and data analysis/interpretation. All authors read and approved the final manuscript.

**Funding:** This study was funded by GlaxoSmithKline plc (HZC113782/NCT01313676).

**Word Count:** (excluding title page, abstract, references, figure legend): 1025/1000

## Introduction

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk for cardiovascular disease (CVD). Those with moderate airflow limitation are more likely to die from CVD than respiratory failure (1). Arterial pulse wave velocity (aPWV), a vascular stiffness marker, is an independent predictor of CVD risk known to be elevated in COPD patients (2). Reduced arterial elasticity plays a direct pathologic role in promoting CVD events. Therefore, decreasing aPWV should lessen future morbidity and mortality. Previous studies addressing whether inhaled therapies for COPD reduce aPWV and adverse cardiovascular (CV) events showed inconclusive results (3–5), perhaps due to inadequate sample sizes or patients were at low CVD risk. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) trial offered a unique study opportunity due to its large patient population and because all patients had a heightened CVD risk. In a pre-defined sub-study, we tested whether aPWV would predict mortality and if inhaled therapy would affect aPWV and several additional metrics of arterial stiffness.

## Methods

### Study Design

SUMMIT was a multicenter, randomized, double-blind, event-driven trial in 16,485 patients (40–80 years) with moderate COPD (mean [ $\pm$ standard deviation {SD}] post-bronchodilator forced expiratory volume in 1 s [FEV<sub>1</sub>] 60 $\pm$ 6% predicted) who had, or were at high-risk ( $\geq$ 60 years with  $\geq$ 2 risk factors) for, CVD (6). The primary endpoint was all-cause mortality (ACM); secondary endpoints were rate of post-bronchodilator FEV<sub>1</sub>

decline and an adjudicated on-treatment CV composite of myocardial infarction, unstable angina, stroke, transient ischemic attack and CV death.

Patients were randomized to once-daily: inhaled placebo (n = 591), long-acting B<sub>2</sub>-agonist (LABA) (vilanterol 25 mcg [VI]; n = 583), corticosteroid (ICS) (fluticasone furoate [FF] 100 mcg; n = 601) or combination therapy (FF/VI; n = 584).

An assessment of arterial stiffness (pulse wave analysis [PWA] and/or carotid-femoral aPWV) were measured with the SphygmoCor (AtCor Medical Inc., Itasca, USA) device in a sub-study of 2,359 patients, of whom 1,788 had acceptable baseline aPWV, with annual measurements for up to 3 years.

The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

### **Statistical Analysis**

Change in aPWV was analyzed using a mixed model repeated measures analysis with fixed effect terms for age, sex, baseline aPWV, study treatment, visit and study treatment by visit. This model was repeated separately for patients with baseline aPWV <11 and ≥11 m/s. This threshold was selected based on published reference values demarcating elevation for patients of similar age (7). Similar analyses were performed on other PWA parameters including central augmentation pressure, or central systolic blood pressure.

Cox proportional hazards analyses of time to death and time to first CV composite event were performed using patients divided into four groups based on their baseline aPWV measurements (quartiles split at 7.4 m/s, 8.8 m/s and 10.7 m/s).

## Results

Demographics of the 2,359 patients in the sub-study were comparable to those of the SUMMIT intent-to-treat efficacy (ITT-E) population: 69% male, with mean $\pm$ SD for age 65 $\pm$ 8 years, post-bronchodilator FEV<sub>1</sub> 60 $\pm$ 6%, and 40 $\pm$ 22 pack-year smoking history, with 49% current smokers. Seventy-two percent had CV disease; the remainder had  $\geq$ 2 CV risk factors in addition to their smoking history.

In the ITT-E population, ACM was unaffected by combination therapy (hazard ratio 0.88, 95% confidence interval [CI], 0.74–1.04;  $P = 0.14$ ) or the individual components. For all treatment groups aPWV remained reasonably stable over the year following the baseline measurement (mean 9.14 m/s), with an overall change of 0.15 m/s, (95% CI, 0.01–0.29 m/s). Conversely, the probability of ACM increased relative to baseline aPWV when presented as quartiles. Patients in the highest quartile group (aPWV >10.7 m/s) had a 90% increase (95% CI, -5–281%) in risk of death versus the lowest quartile group (PWV  $\leq$ 7.4 m/s) (Figure 1). No relationship was found between aPWV and on-treatment CV composite. No treatment affected change in aPWV at 1 year either overall (Figure 2), or when baseline aPWV was dichotomized at 11 m/sec (Table). Similarly, there was no treatment effect on PWA parameters: central augmentation pressure, central augmentation pressure at a heart rate of 75 bpm, or central systolic blood pressure.

## Discussion

In patients with COPD with moderate airflow limitation, with or at high-risk of CVD, baseline aPWV appeared predictive of mortality but was unaffected by therapy. Several studies report an association between impaired pulmonary function and adverse CV outcomes even after adjusting for accepted CV risk factors (8). Mechanisms underlying this association are currently unknown, however recent evidence suggests that systemic inflammation in COPD may promote atherosclerosis (9), supporting a pathogenetic link between these two conditions. Moreover, patients with COPD and biomarkers of persistent inflammation are at greater mortality risk (9). Increased aPWV has been shown to be a predictor of all-cause and CV morbidity and mortality (10) and has been shown to relate to COPD and emphysema severity (11).

ICS/LABA improve lung function and decrease COPD exacerbations. A *post hoc* analysis comparing fluticasone propionate/salmeterol with placebo suggested that the former regimen lowered aPWV at 12 weeks in patients with COPD and moderate airflow limitation (post-bronchodilator FEV<sub>1</sub> 55–56% predicted) with baseline aPWV values >10.9 m/s (3). Similarly, a non-placebo-controlled 12-week trial demonstrated that both FF/VI and tiotropium lowered aPWV by ~1 m/s in patients with COPD (post-bronchodilator FEV<sub>1</sub> 46.5% predicted) with baseline values ≥11 m/s (4). However, a subsequent 24-week trial in patients (post-bronchodilator FEV<sub>1</sub> 50.1% predicted), mean baseline aPWV of 13.26 m/s, failed to demonstrate an effect of FF/VI on aPWV versus placebo and no relationship was observed on aPWV and hsCRP, fibrinogen, IL-6 or PARC (5).

This analysis adds to and confirms previous studies evaluating the impact of treating COPD on co-morbid CV complications. The cumulative data suggest that despite the increased prevalence and importance of CVD disease in patients with COPD, aggressive treatment focusing on improving CVD risk factors is paramount, as inhaled therapy for COPD appears unlikely to reduce the associated heightened CV risk. Smoking is a common risk factor for both COPD and CVD. Future studies investigating smoking-induced inflammation may identify potential pathogenetic links between COPD and CVD, from which the knowledge gained might lead to the development of novel therapies.

**Acknowledgments:** The authors would like to thank the SUMMIT steering committee (6), composed of academic experts and employees from GlaxoSmithKline plc, who were responsible for the scientific oversight, study design and analysis and review and interpretation of the SUMMIT Study.

**Author Disclosures:** CC, JAA and JCY are employees of and hold stock in GlaxoSmithKline plc. NJC is employed by Veramed Ltd, a Contract Research Organization undertaking contracted statistical analyses of studies funded by GlaxoSmithKline plc. PMAC was a past Member of the GSK Steering Committee and was Chair of the Steering Committee at Boehringer Ingelheim. He has also received lecture fees from AstraZeneca. BRC received payments as part of the GSK Scientific Committee. FJM is DSMB chair of the parent study, and serves on the COPD Advisory Boards for AstraZeneca, COPD Study Steering Committee for Boehringer Ingelheim, as a COPD consultant for Proterrix Bio, Asthma study DSMB for Gentech, COPD Advisory Boards and COPD Study Steering Committee for GSK, COPD Advisory Board and



Global disease state presentation for Novartis, and the COPD Advisory Board for Pearl. He is also involved with COPD CME for UpToDate. DEN serves on the Consultancy as part of Trial Steering Committee of SUMMIT. JV is supported by the National Institute of Health Research Manchester Biomedical Research Centre (NIHR Manchester BRC) and has received honoraria from GSK, serves on the Study Steering Committee, and is an Advisor and presenter for AstraZeneca, Boehringer Ingelheim, Chiesi and Novartis. RDB has no conflicts of interest to declare.

**Data Sharing:** Information on GlaxoSmithKline plc's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com).

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## Figure Legends

**Figure 1.** Kaplan-Meier plot of time to on- or post-treatment death by pulse wave velocity quartiles. Reduction in risk, using Quartile group 1 as reference, calculated using Cox-proportional hazard ratios adjusted for age, sex, study treatment, ethnicity, race, BMI category, smoking status, cardiovascular study entry criteria, percent predicted FEV<sub>1</sub>, previous exacerbations, vascular and ischemic indicators and modified MRC dyspnea scale. Reduction in risk=(1-Hazard Ratio)\*100.

**Figure 2.** Adjusted mean change from baseline aPWV over time by treatment category from mixed model repeated measures analysis. FF 100 = fluticasone furoate 100 mcg; aPWV = arterial pulse wave velocity; VI 25 = vilanterol 25 mcg.

**Table.** Mixed Model Repeated Measures Analysis of Arterial Pulse Wave Velocity (m/s) at 1 year by Baseline Arterial Pulse Wave Velocity

	Placebo	FF 100	VI 25	FF/VI 100/25
Number of patients in arterial stiffness sub-study	591	601	583	584
Number of patients with baseline aPWV measurement	454	452	443	439
<b>Patients with baseline aPWV &lt;11 m/s</b>				
Number of patients with data at 1 year	230	242	228	252
Baseline raw mean aPWV, m/s	8.2	8.2	8.0	8.1
Adjusted mean change in aPWV at 1 year, m/s	0.8	0.8	0.5	0.8
<b>Patients with baseline aPWV ≥11 m/s</b>				
Number of patients with data at 1 year	67	61	64	61
Baseline raw mean aPWV, m/s	13.1	12.8	12.9	13.1
Adjusted mean change in aPWV at 1 year, m/s	-2.2	-1.8	-2.0	-1.6

FF = fluticasone furoate; aPWV = arterial pulse wave velocity; VI = vilanterol.

There was little correlation of aPWV with any of the collected biomarkers (r values - 0.07–0.10; all *P*-values ≥0.095).

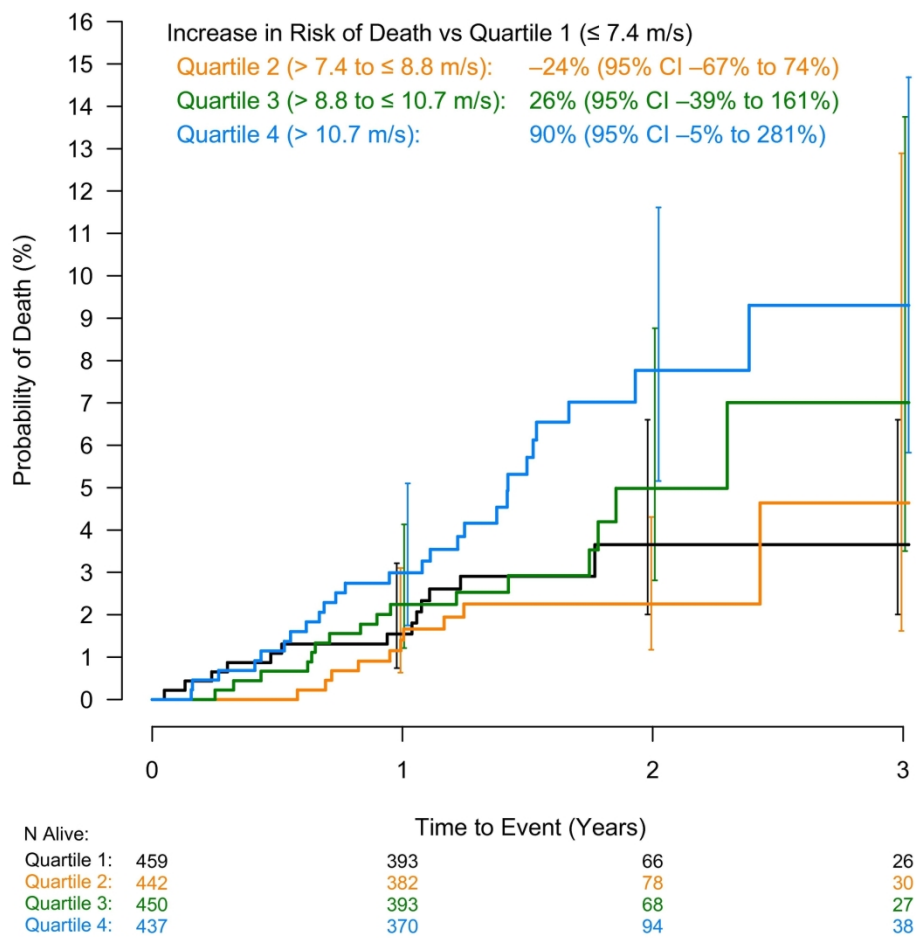


Figure 1. Kaplan-Meier plot of time to on- or post-treatment death by pulse wave velocity quartiles. Reduction in risk, using Quartile group 1 as reference, calculated using Cox-proportional hazard ratios adjusted for age, sex, study treatment, ethnicity, race, BMI category, smoking status, cardiovascular study entry criteria, percent predicted FEV1, previous exacerbations, vascular and ischemic indicators and modified MRC dyspnea scale. Reduction in risk=(1-Hazard Ratio)\*100.

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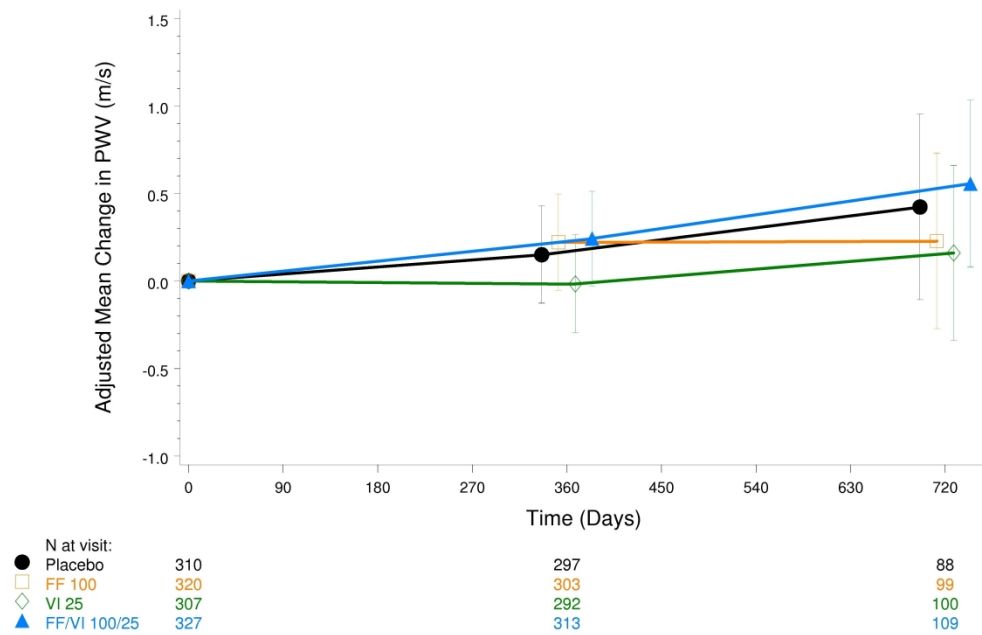


Figure 2. Adjusted mean change from baseline aPWV over time by treatment category from mixed model repeated measures analysis. FF 100 = fluticasone furoate 100 mcg; aPWV = arterial pulse wave velocity; VI 25 = vilanterol 25 mcg.

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